Developing health economic models of chronic diseases for reimbursement purposes

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Long-Term Clopidogrel Therapy in Patients Receiving Percutaneous Coronary Intervention

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Abstract

Background: The PCI-CURE (Percutaneous Coronary Intervention-Clopidogrel in Unstable Angina to Prevent Recurrent Events) and CREDO (Clopidogrel for the Reduction of Events During Observation) studies have demonstrated that, in addition to aspirin, pre-treatment with clopidogrel followed by long-term (i.e. 9–12 months) therapy significantly reduces the risk of atherothrombotic events in patients undergoing percutaneous coronary intervention (PCI).

Objective: To examine the economic implications, from the Dutch healthcare perspective, of the use of clopidogrel in patients undergoing PCI (elective procedures or in patients with acute coronary syndrome), comparing pre-treatment followed by long-term therapy with only 4 weeks of treatment.

Methods: A lifetime Markov model was used to combine data from the PCICURE and CREDO trials with data from the literature concerning epidemiology, costs and quality of life. The model was run separately for each trial. Only direct healthcare costs (€, year 2004 values) were considered. Costs and outcomes were discounted at 4% per anum. For each trial, the cost effectiveness is expressed as costs per life-year and QALY gained. Uncertainties are addressed by uni- and probabilistic multivariate sensitivity analysis. Results: When starting with the data from the PCI-CURE trial, pre-treatment plus 9-month clopidogrel therapy was predicted to save €1119 and gain 0.03 life-years and 0.07 QALYs per patient compared with short-term treatment. When starting with the data from the CREDO trial, the combination of pre-treatment and prolonged clopidogrel therapy (1 year) was estimated to save €497 and gain 0.10 life-years and 0.14 QALYs per patient. Univariate and probabilistic multivariate sensitivity analyses suggested that the conclusions were generally robust, but that the expected gain in survival for the PCI-CURE population was very sensitive to the effects on mortality within the combined endpoint of myocardial infarction/ stroke-free survival.

Conclusions: In The Netherlands, pre-treatment plus long-term (9–12 months) therapy with clopidogrel is estimated to save costs and increase (quality-adjusted) survival in the prevention of ischaemic events among patients undergoing elective PCI (CREDO) and in patients with acute coronary syndrome (PCI-CURE) compared with short-term treatment with clopidogrel without pre-treatment.

Introduction

The PCI-CURE (Percutaneous Coronary Intervention-Clopidogrel in Unstable Angina to Prevent Recurrent Events) study recently demonstrated that treatment with clopidogrel before PCI in patients with acute coronary syndrome (ACS) followed by prolonged clopidogrel (75mg daily) for 9 months (long-term clopidogrel) after PCI was superior to no pre-treatment followed by short-term (4 weeks) clopidogrel (all added to aspirin therapy).[1] From the moment of randomisation (including the time before PCI) the number of patients who experienced a myocardial infarction (MI) or died was 116 in the long-term and 169 in the short-term clopidogrel group, representing a relative risk reduction of 31% and an absolute risk reduction of 3.4%. Safety out-comes did not differ significantly.[1]

Where the PCI-CURE trial concerned patients with ACS, more recently a similar trial (CREDO; the Clopidogrel for the Reduction of Events During Observation) was performed concerning patients undergoing elective PCI. The CREDO trial com-pared a loading dose of clopidogrel prior to PCI followed by clopidogrel treatment for 1 year with no loading dose and short-term (4 weeks) clopidogrel therapy, all added to aspirin therapy.[2] Long-term clopidogrel therapy was associated with a 26.9% (95% CI 3.9, 44.4; p = 0.02) reduction in the relative risk and a 3% reduction in the absolute risk of the combined endpoint of death, MI and stroke at 1 year.

However, in the patient group treated with clopidogrel for 1 year, an increase in major bleeding was observed (8.8% long-term clopidogrel therapy vs 6.7% short-term clopidogrel therapy; p = 0.07).[2] The demographics of the patient populations included in CREDO and PCI-CURE are presented in table I.[1,2]

Table I. Demographics of patients in CREDO and PCI-CURE[1,2]

Demographics	CREDO		PCI-CURE	
	clopidogrel	placebo	clopidogrel	placebo
n	1053	1063	1313	1345
Mean age [n (SD)]	61.5 (11.2)	61.8 (11.0)	61.6 (11.2)	61.4 (10.9)
Women (%)	29.3	27.9	30.3	30.1
Diabetes (% of pts)	27.5	25.4	19.0	19.0
Previous MI (% of pts)	33.5	34.4	27.3	26.0
Previous PCI (% of pts)	85.6	86.2	13.4	13.8
Previous CABG (% of pts)	3.9	4.0	12.0	13.0
Smokers (% of pts)	32.2	29.4	30.9	29.5

CABG = coronary arterial bypass grafting; **MI** = myocardial infarction; **PCI** = percutaneous coronary intervention.

Long-term treatment with clopidogrel may increase the direct costs of treatment and consequently, questions may be asked about the balance between costs and effects. The purpose of this study was to estimate the lifetime costs and effects of long-term clopidogrel treatment after a PCI. This was done by using a model that was used to support the Dutch guidelines about statin-therapy, anti-hypertensive therapy and the recent guidelines about cardiovascular risk management.[3-5] The model starts by deriving cardiovascular risk-profiles

and efficacy parameters (transition probabilities) and extrapolates those on the basis of epidemiological data. Predictions are made for survival and the occurrence of events that are combined with estimates currence of events that are combined with estimates run in two distinct patient populations: in those with ACS (using the cardiovascular risk profiles and efficacy parameter data from the PCI-CURE trial) and in patients undergoing elective PCI (using the transition probabilities from the CREDO trial).[1,2]

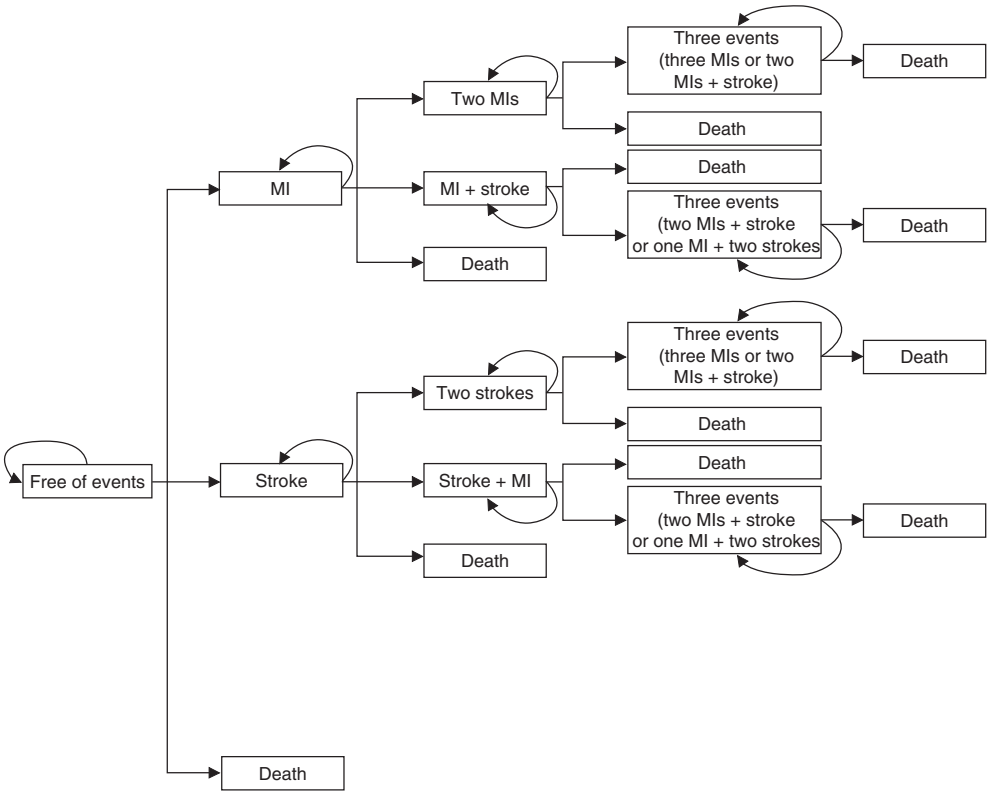

Fig. 1. Overview of Markov model structure and of health states incorporated in the model. **MI** = myocardial infarction.

Methods

A Markov model[6] was adapted[7] to simulate the life expectancy, QALY and costs of patients with varying cardiovascular risk profiles. Consistent with the PCI-CURE and the CREDO trials, pre-treatment with clopidogrel followed with 9- and 12-month clopidogrel therapy was compared with short-term (4 weeks) clopidogrel therapy, respectively. The model

was run separately for the PCI-CURE and CREDO populations.[1,2] The analysis was performed from the Dutch perspective and included direct healthcare costs only. As indicated by the Dutch Guidelines for Pharmacoeconomic Research,[8] future costs and effects were

discounted at the rate of 4% per annum. All costs were expressed in € (year 2004 values). The model was built using Microsoft Excel™.

Model Structure

As the model concerns a chronic disease, it adopts a lifetime (i.e. 50 years) perspective to estimate the benefits and costs of clopidogrel therapy. Figure 1 provides a simplified presentation of the model. All patients entering the model wee initially 'free of events'. As patients aged during the 50-year simulation, they died, remained free of events, developed a first MI, developed a first stroke, devel oped recurrent MI or stroke, or developed a combi ation of strokes and MIs. These events were assumed to occur every 6 months, reflecting the cycle length used in the model. Patients who have experienced a first stroke or MI continue to be exposed to the risk of subsequent strokes or MIs, with a maximum of three non-fatal events (one stroke and two MIs, two strokes and one MI, three MIs or three strokes). The model distinguished between three sub-states within each health state (not shown in figure 1), defined as the first 6 months, the second 6 months and subsequent 6-month periods. This distinction was introduced to allow for transition probabilities and costs to vary with time elapsed since therapy initiation. The occurrence of PCIs and coronary artery bypass grafts (CABGs) was included in the estimates of costs. However, these events are not presented in figure 1.

Probabilities of Events

For the first year of the analysis, all probabilities (e.g. risk of MI, death from MI, stroke, death from stroke, cardiovascular death and other death) were derived from the intent-to-treat analyses of the PCI-CURE (including events before PCI) and CREDO trials.[1,2] However, the results from both trials indicated that there is a decrease in the underlying risk of events in the first year. To capture this, Weibull survival models were fitted over the event rates at 1 month and at end of follow-up.[1,2] The Weibull scale (β) parameter depends on the Weibull shape (α) parameter and survival. Survival rates at day 30 and at end of follow-up are known. Hence, by using the 'goal seek' function in Excel™ to vary α to find the β at which β30 and β365 are equal, the Weibull's function α and β can be specified. Based on the event-specific Weibull models, the individual event probabilities during the first and second 6 months were derived (see the supplementary material ['ArticlePlus'] at http://pharmacoeconomics.adisonline.com). Table II shows the resulting transition probabilities for both trials. No initial estimate was available from the PCI-CURE study[1] of the risk of stroke and death from stroke as it was not included as an endpoint. There fore, the number of (fatal) strokes for the PCI-CURE analysis was derived from the overall CURE trial.[10] The latter trial showed that 1.3% of the patients experienced a stroke in 1 year. The number of (fatal) strokes in both treatment arms was derived from the ratio of fatal and non-fatal strokes shown in the same trial. The

corresponding transition probabilities for non-fatal and fatal stroke during long- and short-term clopidogrel therapy are presented in table II.

Both the PCI-CURE and CREDO trials reported the numbers of revascularisations without a distinction between PCIs and CABGs. It was estimated that for every one CABG, there would be 1.7 PCIs, reflecting the ratio of these revascularisation events observed during initial hospitalisation in the entire (not only PCI-CURE) CURE database.[10] Further-more, bleeds, PCIs and CABGs were only included in the model for the duration of the trials. After this, treatment does not differ, and later differences in relationship to the earlier treatment are assumed to be non-existent.

Table II. Transition probabilities (by study and 6-month period)[a]

Event[b]	First 6 months		Second 6 months	
	clopidogrel	aspirin	clopidogrel	aspirin
PCI-CURE				
MI	6.61 (5.33, 8.01)	9.99 (8.44, 11.64)	0.71 (0.33, 1.24)	1.10 (0.61, 1.72)
Stroke	1.00 (0.54, 1.59)	1.00 (0.54, 1.59)	0.11 (0.00, 0.34)	0.11 (0.00, 0.34)
Fatal MI	0.82 (0.55, 1.62)	0.52 (0.21, 0.97)	0.09 (0.00, 0.30)	0.06 (0.00, 0.24)
Fatal stroke	0.15 (0.02, 0.41)	0.15 (0.02, 0.41)	0.02 (0.00, 0.12)	0.02 (0.00, 0.12)
Other CV death	1.21 (0.70, 1.87)	1.36 (0.81, 2.04)	0.13 (0.01, 0.39)	0.15 (0.02, 0.45)
CABG[c]	5.24 (4.04, 6.45)	6.33 (4.98, 7.67)		
PCI[c]	8.92 (7.38, 10.46)	10.77 (9.02, 12.53)		
Bleeds[c]	2.74 (1.86, 3.63)	2.45 (1.62, 3.29)		
CREDO				
MI	6.19 (4.81, 7.72)	8.11 (6.6, 9.8)	1.01 (0.5, 1.69)	1.34 (0.74, 2.11)
Stroke	0.46 (0.14, 0.94)	0.99 (0.49, 1.7)	0.07 (0.00, 0.24)	0.16 (0.02, 0.48)
Death MI	0.36 (0.09, −0.81)	0.27 (0.05, 0.67)	0.06 (0.00, 0.21)	0.04 (0.00, 0.17)
Death stroke	0.36 (0.09, −0.81)	0.09 (0.00, 0.34)	0.06 (0.00, 0.21)	0.02 (0.00, 0.09)
Other CV death	0.91 (0.43, 1.57)	1.85 (1.10, 2.72)	0.15 (0.01, 0.45)	0.31 (0.07, 0.71)
CABG[c]	7.91 (6.27, 9.53)	7.76 (6.08, 9.43)		
PCI[c]	13.46 (11.41, 15.53)	13.21 (11.04, 15.41)		
Bleeds[c]	8.83 (7.12, 10.55)	6.68 (5.13, 8.23)		

a Figures presented as % (95% confidence interval).

b Risk of other death was derived from the Central Bureau of Statistics[9] for non-cardiovascular death for men aged between 60 and 64 years.

c These events were assumed to occur only during the trial duration.

CABG = coronary arterial bypass grafting; **CV** = cardiovascular; **MI** = myocardial infarction; **PCI** = percutaneous coronary intervention.

It was assumed that patients in both treatment arms would be treated with aspirin only after 1 year. Hence, the second half-year transition probabilities of the aspirin treatment arm are applied in later years in both treatment arms, albeit that those transition probabilities are corrected for the increase in age.

Precise estimates of the increased risks of events due to ageing are not available. Several sources were consulted to estimate epidemiological parameters. The annual age-specific increases in the probability of experiencing a first non-fatal or fatal stroke were estimated at 8% and 6%, respectively, based on the Rotterdam study.[11] The age-specific increases in the probability of a MI, fatal MI or other vascular death were assumed to be equal to the age-

specific increase in the probability of having a stroke. This choice is substantiated by Koek et al.[12] and by the risk equations from the Framingham population.[12] The annual increase in mortality from non-cardiovascular causes was 10%, consistent with the Dutch mortality pattern.[9]

Furthermore, the transition probabilities of ex periencing a subsequent event after having an initial event were based on the initial event probabilities for the second half-year. These probabilities have been adjusted using relative risks that reflect the fact that every event increases the risk of subsequent events.[13] These relative risks were chosen such that they reflect the following (see the supplementary material):

- On the basis of the CURE data, patients with previous events were at increased risk of subsequent events, especially in the first 6 months after study entry.[13]
- The probability of the same event (e.g. MI) occurring was assumed to be higher than the probability of a different event occurring.[14]
- The probability of a vascular event was assumed to increase with the number of prior events.
- The relative risks were quantified such that the modelled life expectancy would reflect the life expectancy as reported in the CAPRA (CAPRIE [Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events] Actual Practice Rates Ana lysis) for the average CAPRIE patient. Also, such that the modelled life-years gained due to avoiding events would be half that as reported in CAPRA (see the supplementary material).[15] The CAPRA analysis reported the life expectancy after an MI, stroke, two MIs and two strokes for patients from Saskatchewan (Canada) who were similar to the CAPRIE population.[15] Due to lack of similar data regarding PCI-CURE and CRE-DO patients, these relative risks were applied in the present analyses.[1,2]

The modelled life expectancy was estimated at approximately 12 and 13 years for CREDO and PCI-CURE, respectively. This reasonably corresponds with the age- and gender-adjusted life expectancy derived from the Framingham study of approximately 14.1 years for patients with coronary heart disease and 11.0 years for patients with an MI.[10] This comparison can be considered a form of external validation of the model's outcomes.

Costs Inputs

Table III presents the cost associated with each specific health state. The costs in the first 6 months included the cost of acute care. Cost estimates were based on previous studies that describe the costs of stroke and MI for the Dutch healthcare setting.[16-18] All costs were converted to year 2004 values using appropriate price indices and rounded to units of €250. The costs of aspirin and clopidogrel were derived from the Dutch 2004 Pharmacopoeia.[19]

QALY Inputs

The treatment effects were expressed in terms of life-years gained and QALYs, calculated as the product of the number of life-years and the estimated utility in a health state. Relative utility values (compared with a healthy person of similar age) for patients after MI[20-22] or stroke[23,24] were based on the literature. Utility values after multiple events were assumed to be equal to the product of the utilities after single events (i.e. for patients experiencing two MIs, this would result in a utility of 0.83 [0.91 × 0.91]). The utility estimates associated with the health states in the model are presented in table III.

Table III. Cost (€, year 2004 values) and utility inputs for model events

Event	Utility	Costs[a]
Aspirin (per day)		0.12
Clopidogrel (per day)		1.87
CABG		10 250
PCI		3 000
Major bleeding		4 000
MI first 6 months	0.91	10 250
MI second 6 months	0.91	2 500
MI after first year	0.91	1 750
Stroke first 6 months	0.66	17 750
Stroke second 6 months	0.66	6 750
Stroke after first year	0.66	4 500
MI + stroke first 6 months	0.60	14 000
MI + stroke second 6 months	0.60	6 750
MI + stroke after first year	0.60	4 500
Fatal MI	0.00	1 500
Fatal stroke	0.00	3 250
Other vascular death	0.00	1 000

a Costs after the second MI were assumed to be equal to those after first MI. Costs after the second stroke and three events were assumed to be equal to those after the first stroke. Cost of other death was assumed equal to the cost of other vascular death. All estimates of the unit costs were varied between 0.75 and 1.25 of their base-case values by means of Uniform distributions.

CABG = coronary arterial bypass grafting; **MI** = myocardial infarction; **PCI** = percutaneous coronary intervention.

Cost-Effectiveness Measures

Cost-effectiveness ratios were expressed as inincremental cost per life-year gained (primary outcomes measure) and incremental cost per QALY gained (secondary outcome).

Sensitivity Analyses

To determine the impact of varying model assumptions on the results, several sensitivity analyses were conducted. First, in the deterministic sensitivity analyses, all base-case cost estimates and agespecific increases in risk-of-events were multiplied by 0.75. Additionally, all

relative risks of experiencing subsequent events were multiplied by 0.50. Sensitivity analyses were also performed, in which the first and second half-year event probabilities per event in the clopidogrel arm were estimated at the upper limit of the confidence interval. Hence, these analyses are univariate worst-case analyses. The relative utility values were set at the highest values reported for the single events,[20-24] which was 0.93 for MI and 0.91 for stroke. Hence, the number of potential QALYs gained by avoiding events is reduced. The impact of using the Dutch ratio of PCI/CABGs (e.g. 3.7 : 1) instead of the ratio observed in CURE (1.7 : 1) was also assessed.[25] The costs and effects of a half-year clopidogrel therapy vs clopidogrel therapy for the full trial duration were also analysed.

Table IV. Estimated discounted incremental costs (€, year 2004 values) and QALYs over time for the PCI-CURE and CREDO models

Resource	1 year		5 years		50 years	
	control	active	control	active	control	active
PCI-CURE						
Costs						
Medication	92	470	216	599	380	770
Post-first MI	1 136	753	3 023	2 361	6 723	6 024
Post-first stroke	210	214	708	726	1 967	2 029
Later events	75	51	1 148	883	8 447	7 730
CABG/PCI	972	805	972	805	972	805
Bleed	98	110	98	110	98	110
Death	50	52	162	162	719	718
Total	2 634	2 455	6 327	5 645	19 306	18 186
QALY						
Medication	0.88	0.91	3.60	3.74	7.21	7.50
Post-first MI	0.07	0.04	0.39	0.29	0.98	0.86
Post-first stroke	0.00	0.00	0.03	0.03	0.11	0.11
Later events	0.00	0.00	0.11	0.08	0.98	0.88
Total	0.96	0.96	4.13	4.15	9.27	9.34
CREDO						
Costs						
Medication	93	624	216	752	362	912
Post-first MI	960	733	2 842	2 488	6 315	6 019
Post-first stroke	216	99	812	548	2 237	1 891
Later events	79	59	1 331	1 098	9 071	8 555
CABG/PCI	1 192	1 214	1 192	1 214	1 192	1 214
Bleed	267	353	267	353	267	353
Death	51	51	177	176	729	732
Total	2 858	3 133	6 837	6 629	20 173	19 677
QALY						
Medication	0.89	0.92	3.60	3.74	6.81	7.07
Post-first MI	0.05	0.04	0.33	0.29	0.83	0.78
Post-first stroke	0.00	0.00	0.04	0.02	0.12	0.10
Later events	0.00	0.00	0.11	0.09	0.91	0.86
Total	0.95	0.96	4.09	4.14	8.67	8.81

CABG = coronary arterial bypass grafting; **MI** = myocardial infarction; **PCI** = percutaneous coronary intervention.

Second, probabilistic multivariate sensitivity analyses were performed. The uncertainty surround ing the estimated proportions of events was mod elled by β distributions, bounded

by 0 and 1. As such the transition-probabilities only vary within their theoretical range and account is taken of the number of observations. For example, if 5 of 50 patients had an event, the 95% confidence interval was estimated at (0.0308, 0.1789). If 20 of 200 patients had an event, the 95% confidence interval was estimated at (0.0567, 0.1322). The distributions of uncertainty for the first and second 6-month probabilities were considered independent.

All estimates of the unit costs, increases in age specific risk of events and the ratio of the number of CABG/PCI performed, were varied between 0.75 and 1.25 of their base-case values by means of Uniform distributions. Relative risks of experiencing subsequent events (compared with a first event) were varied between 0.5 and 1.5 of initial values, again using Uniform distributions. The latter interval was wider because of the uncertainty surround-ing the relative risks. Uniform distributions were used as the standard errors surrounding costs, age specific increases in risk of events and the relative risks were unknown.

For the probabilistic analyses, the model simulat ed 1000 different cohorts by using Monte Carlo Simulation.[26] These simulations were performed using the @Risk 4.5™ software. The results from the generated 1000 cohorts are summarised by picturing average costs and effects in a cost-effectiveness plane and by calculating acceptability curves.[27] Both results give an indication of the uncertainty surrounding the central estimate of the cost-effectiveness ratio. The points in the cost-effectiveness plane may be used to calculate ellipses that represent the smallest area holding a fixed percent age of the probability that both costs and effects are located within that area. The acceptability curve measures (on the vertical axis) the probability that the cost-effectiveness ratio is under a certain threshold (on the horizontal axis).

Results

PCI-CURE Population

For patients in the long-term clopidogrel therapy arm, the average discounted lifetime costs and effects per patient were estimated at €18 186, 9.78 life-years and 9.34 QALYs. The corresponding figures for the short-term clopidogrel therapy arm were €19 306, 9.76 life-years and 9.27 QALYs. The expected incremental cost saving, life-years gained and QALYs were therefore estimated at €1119, 0.03 life-years and 0.07 QALYs. The number needed to treat to avoid one event during the treatment period was estimated at 29. The costs and effects over time per cost item are presented in table IV. Clopidogrel was estimated to be cost saving within 1 year of treatment.

The result of the sensitivity analysis with respect to the epidemiologic parameters and the parameters of costs and QOL show that the estimated incremental costs and effects were robust over the entire range of the univariate sensitivity analyses (table V).

The same conclusion cannot be drawn with respect to the uncertainty surrounding the transition probabilities to experience a first event during the first and second 6 months. The

uncertainty surrounding the cost per life-year gained was presented using ellipses (figure 2). Although there was a 98% probability that long-term clopidogrel therapy is cost saving, there was only a 65% probability that it is more effective in terms of saving life-years and QALYs.

Table V. Results of univariate sensitivity analyses on base-case discounted incremental lifetime costs (€, year 2004 values), life expectancy, QALYs and incremental cost-effectiveness ratios (ICERs) for the PCI-CURE and CREDO models

Parameter	PCI-CURE				CREDO			
	costs	LY	QALY	cost/LY	costs	LY	QALY	cost/LY
Base case	−1 119	0.03	0.07	Dominant	−497	0.10	0.14	Dominant
Costs of health states reduced by 25%	−781	0.03	0.07	Dominant	−208	0.10	0.14	Dominant
Utility stroke 0.91 and utility MI 0.93	−1 119	0.03	0.06	Dominant	−497	0.10	0.12	Dominant
Risk of subsequent event reduced by 50%	−1 133	0.00	0.04	Dominant	−564	0.08	0.12	Dominant
% increase with age reduced by 25%	−1 185	0.03	0.08	Dominant	−550	0.11	0.15	Dominant
Dutch ratio PCI/CABG (e.g. 3.7 : 1)	−1 086	0.03	0.08	Dominant	−501	0.11	0.15	Dominant
Discount rate 0%	−1 341	0.05	0.11	Dominant	−628	0.15	0.19	Dominant
Discount rate 7%	−994	0.02	0.05	Dominant	−414	0.08	0.11	Dominant
Trial duration clopidogrel vs half-year clopidogrel therapy	109	0.003	0.007	36 148	159	0.013	0.018	12 030
Upper-limit CI clopidogrel probabilities								
MI	−457	0.01	0.03	Dominant	193	0.07	0.09	2 819
stroke	−407	0.02	0.04	Dominant	655	0.09	0.09	7 360
death MI	−1 245	−0.07	−0.03	NA[a]	−580	0.05	0.09	Dominant
death stroke	−1 158	−0.01	0.04	NA	−569	0.05	0.09	Dominant
other vascular death	−1 236	−0.06	−0.01	NA	−633	0.02	0.06	Dominant

a NA because these ICERs would concern the cost effectiveness of aspirin compared with clopidogrel instead of the reverse.

CABG = coronary arterial bypass grafting; **CI** = confidence interval; **LY** = life-year; **MI** = myocardial infarction; **NA** = not applicable; **PCI** = percutaneous coronary intervention.

The 35% probability of clopidogrel being less effective may seem surprising in light of the significant relative risk reduction in the combined endpoint of MI and death; however, the cost savings were mainly driven by a reduction in non-fatal MIs and not by a reduction in deaths, mortality being even slightly higher in the clopidogrel arm (see table II). The deterministic sensitivity analyses confirmed these findings and show that the number of life-years saved is very sensitive to changes in the probability of dying from cardiovascular causes (table V). The acceptability curve (figure 3) presents the probability of cost effectiveness for varying will ingness to pay (WTP) for a year of life gained. Consistent with the results shown in figure 2, there was a 98% chance that clopidogrel is cost saving. Further, at a WTP threshold of €20 000 for a year of life gained, the probability of cost effectiveness was 87%. This probability decreased slightly to approximately 75% when the WTP per life-year gained increased to €50 000.

CREDO Population

In the CREDO population, the average discounted lifetime costs and effects per patient were estimated at €19 667, 9.26 life-years and 8.81 QALYs for patients in the long-term clopidogrel therapy arm. The corresponding figures for the short-term clopidogrel therapy arm were €20 173, 9.16 life-years and 8.67 QALYs. The incremental discounted savings per patient were

estimated at €497, and 0.10 life-years and 0.14 QALYs were saved per patient. Table IV shows that the model predicts that clopidogrel is not cost saving in the first year, but that, when the long-term consequences are taken into account, treatment will become cost saving. These results were robust over the entire range of univariate sensitivity analyses (table V). Longterm clopidogrel therapy was more effective in 99% and cost saving in 99% of the 1000 Monte Carlo simulation runs (figure 4). At €20 000 per life-year gained, the probability that long-term clopidogrel was cost effective was 99% (figure 5).

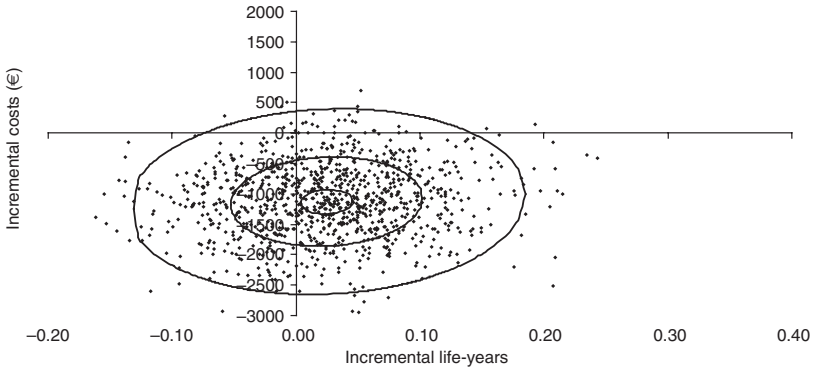

Fig. 2. Elliptical contours of incremental cost (year 2004 values) and life-years for the PCI-CURE population. The 95%, 50% and 5% elliptical contours (from outer to inner ellipses) envelop 95%, 50% and 5%, respectively, of 1000 Monte Carlo Simulation (MCS) runs (each represented by a dot). The larger portion of the ellipses overlaps on the lower right side of the figure, where the MCS runs suggest the use of long-term clopidogrel both saves costs and increases life expectancy.

Discussion

The purpose of this study was to examine the cost effectiveness of a loading dose of clopidogrel before PCI followed by long-term clopidogrel and aspirin therapy (9–12 months) versus short-term treatment (4 weeks) with clopidogrel from the Dutch healthcare perspective. The data from two trials were combined with a model capturing expectations about epidemiology, costs and QOL. The results suggest that, against the background of aspirin therapy, more intense treatment saves costs and increases survival.

The analysis starts with the efficacy of treatment observed in the PCI-CURE and CREDO trials.[1,2] In doing so it does not ask the question whether the benefits generated by clopidogrel are caused by the loading dose or the long-term treatment. Eriksson[28] suggests that the benefits are mainly related to the loading dose and that one might suggest that this loading dose is extremely cost effective and that long-term treatment is not. In the sensitivity analyses, comparing clopidogrel therapy for the full trial duration with a half-year, the cost effectiveness of treatment for the full trial duration compared with a half-year was estimated at €36 148 and €12 030 per life-year gained in PCI-CURE and CREDO, respectively.

The paper adds to the literature, in that no previous English paper describing the model has been published in an international peer-reviewed journal, and the cost effectiveness of clopidogrel in the PCI-CURE and CREDO trials has not previously been analysed for the Dutch healthcare setting.[1,2] Earlier applications of the model concern supportive calculations for the development of Dutch guidelines concerning statin-therapy, anti-hypertensive therapy and, recently, cardiovascular risk management.[3-5] This model has also been used in an analysis conducted in the context of an application to reimburse clopidogrel

in The Netherlands.[29,30] The results of the latter analysis were similar to those of a Swedish study.[31] The model was also used to estimate the cost effectiveness of clopidogrel in high-risk CAPRIE subgroups in Denmark.[7]

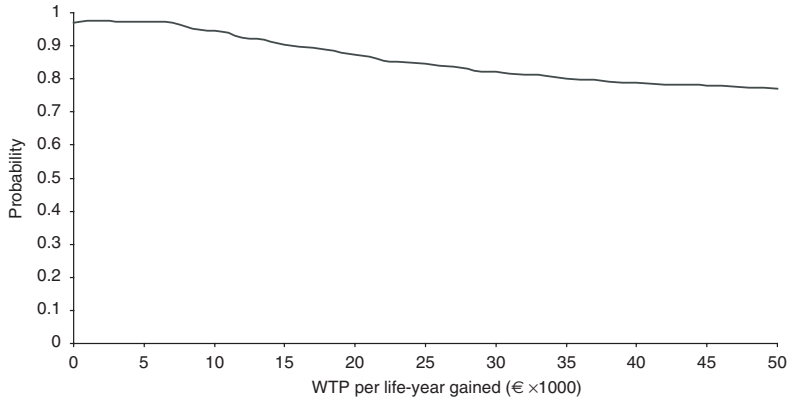

Fig. 3. Cost effectiveness acceptability curve for the PCI-CURE population. The acceptability curve presents the probability that long-term clopidogrel therapy is cost effective given various willingness-to-pay (WTP) thresholds for a year of life. For instance, for a WTP threshold of €20 000, the probability that long-term clopidogrel is cost effective is approximately 87%.

Annemans et al.[32] showed cost savings for longterm clopidogrel therapy in the within-trial analysis of the PCI-CURE study in The Netherlands. Lindgren et al.[33] recently demonstrated that, from a societal perspective, when applying a long-term time horizon, 9-month clopidogrel therapy plus aspirin appeared to be cost effective in a model analysis of patients with unstable coronary artery disease undergoing PCI in Sweden. The latter model predicted an increase of 0.04 years in survival for the clopidogrel treatment arm versus the placebo arm, whereas in a long-term model Weintraub et al.[34] predicted a 0.10-year gain in survival. Our model predicted a 0.04-year increase in survival. Adopting a Swedish cost perspective, Lindgren et al.[33] also estimated an increase of €449 in direct costs associated with clopidogrel in the PCI-CURE patient population. In contrast, our model predicts that long-term clopidogrel treatment is cost saving. This difference may be explained by a difference in price of clopidogrel, as Lindgren et al.[33] used a price of €700, whereas the present model used a

price of €600 for the treatment duration. Differences in modelling structures and assumptions may also partly explain the differences. The model by Lindgren et al.[33] only considered MIs occurring 7 days after admission, and considered only MI and death and ignored the risk of subsequent events after an initial MI. In addition, our model included revascularisations and bleeding episodes, and the increased risk of subsequent events. Moreover, Lindgren et al.[33] incorporated data from a registry of coronary care patients (the Swedish Register of Information and Knowledge about Swedish Heart Intensive care Admissions; RIKS-HIA) and applied the relative risk found in PCI-CURE to quantify the long-term impact of clopidogrel. Our model used the event rates as presented in the PCI-CURE publication.[1] Furthermore, the Lindgren et al.[33] model used lower unit costs for first and subsequent years after an MI.

Using the per-protocol CREDO trial data,[2] Cowper et al.[35] estimated that long-term clopidogrel therapy would cost $US15 696 per life-year saved in the US (year 2000 values). This is an acceptable cost-effectiveness ratio in Western countries, but it is significantly less favourable than the dominance (cost saving and more effective) reported in this paper. The difference between our results and those of Cowper et al.[35] may be explained by a difference in costs for clopidogrel. Cowper et al.[35] used a price of $US3.22 per day, with a monthly dispensing fee of $US2.50, whereas the present model used €1.87 per day. Further differences are seen in the modelling approach. Cowper et al.[35] used a decision tree, which did not consider the increased risk of subsequent events (e.g. MI, stroke) over time after experiencing an event. In contrast, we used a Markov model and considered the effect of increased risk of subsequent events over time. Accordingly, avoiding one MI in our model may result in subsequent avoidance or delay of possible additional events (i.e. MI, stroke and fatal cardiovascular events). In addition to regional differences, our model used the baseline characteristics and event rates form the intention-to-treat analysis presented in CREDO,[2] whereas Cowper et al.[35] relied on the Duke information system of cardiovascular diseases and the CREDO per-protocol data.[2] An economic analysis of the CREDO trial has also been published recently.[36] Compared with another previously published study, the study at hand indicates larger overall cost savings with the use of clopidogrel.[36] This is likely explained by the substantially higher initial event costs in The Netherlands for an MI applied in the present model com pared with the Swedish MI costs applied in the model by Ringborg et al.[36]

Study Limitations

This study was based on the results of two clinical trials. The limitations of those trials are also applicable to our analysis.[28] For instance, both the CREDO and PCI-CURE trials took place before the introduction of the drug-eluting stent.[1,2] However, the benefits of long-term clopidogrel use may be greater with drug-eluting stents, given the risk of late stent thrombosis.[37] As the sources for the unit costs were somewhat dated, broad ranges, e.g. 25%, surrounding unit costs were assumed in the sensitivity analyses. The latter did not affect the paper's conclusions. Data on non-healthcare costs (e.g. travel, informal care and productivity

losses) were not available and were therefore not included in the present analysis. However, since these costs are associated with the occurrence of events and the frequency of events is lower with long-term clopidogrel therapy, it is fair to assume that the cost of long-term clopidogrel therapy would likely be further diminished. However, these additional savings are likely modest as patients at the time of initiation of therapy were aged approximately 61.5 years.[1,2]

In the model, it is assumed that life-years saved due to avoiding strokes and MIs in the CAPRIE population[13] resemble the life-years saved due to avoiding strokes and MIs in the PCI-CURE and CREDO populations.[1,2] As the relative risks were extrapolated to the PCI-CURE and CREDO populations,[1,2] in the multivariate sensitivity analyses, the uncertainty surrounding these relative risks was assumed considerable, e.g. between 0.5 and 1.5 of the base-case values. This did not affect the conclusions in the univariate and multivariate sensitivity analyses.

Furthermore, since the CAPRA study, the quality of care may have increased.[15] Therefore, the model might underestimate overall survival and perhaps also life-years lost due to subsequent events. With respect to the latter, as the relative risks were chosen such that the life-years gained in the model would be half that observed in CAPRA, it may be expected that the impact by the model-estimated incremental life-years falls within acceptable ranges.

An analysis on the influence on the costs and effects of a potential rebound effect after stopping clopidogrel therapy was not performed, as clear evidence is lacking for such an effect.

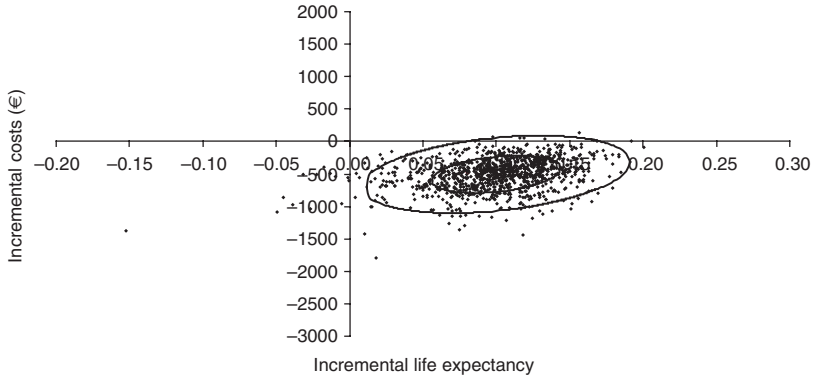

Fig. 4. Elliptical contours of incremental cost (year 2004 values) and life-years for the CREDO population. The 95%, 50% and 5% elliptical contours (from outer to inner ellipses) envelop 95%, 50% and 5%, respectively, of 1000 Monte Carlo Simulation (MCS) runs (each represented by a dot). The larger portion of the ellipses overlaps on the lower right side of the figure, where the MCS runs suggest the use of long-term clopidogrel both saves costs and increases life expectancy.

In the probabilistic multivariate sensitivity analyses, all events of long-term therapy and placebo therapy during both the first and second 6-month periods were simulated individually without taking into account of any correlations that may naturally exist between individual events during these periods and between different events (e.g. stroke and MI). As such, the ellipses presented in figures 2 and 4 over-estimate the uncertainty surrounding the out comes.

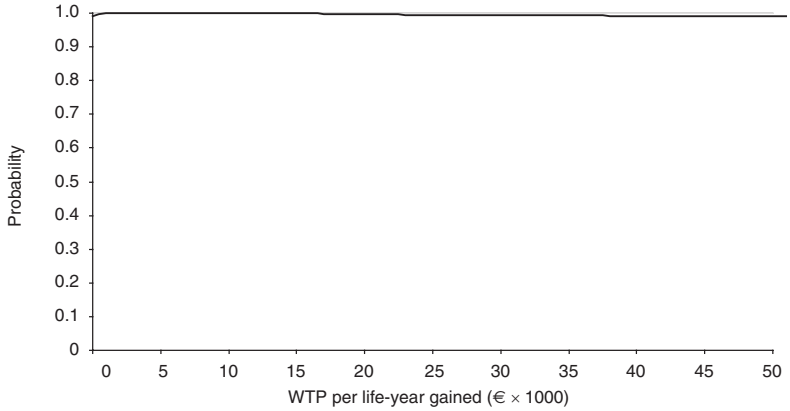

Fig. 5. Cost effectiveness acceptability curve for the CREDO population. The acceptability curve presents the probability that long-term clopidogrel therapy is cost effective given various willingness-to-pay (WTP) thresholds for a year of life. For instance, for a WTP threshold of €20 000, the probability that long-term clopidogrel is cost effective is approximately 99%.

Conclusion

This analysis suggests that in The Netherlands a loading dose of clopidogrel before PCI followed by long-term therapy (9–12 months) is dominant (cost saving and more effective) for the prevention of subsequent ischaemic events in patients undergoing either an elective procedure (CREDO) or in patients with ACS (PCI-CURE) compared with short-term treatment with clopidogrel without a bolus dose. For the CREDO population, the extensive sensitivity analyses suggest that this conclusion was robust, but for the PCI-CURE population the sensitivity analyses suggest that the expected gain in survival was STvery sensitive to the effects on mortality within the combined endpoint of MI-free survival.

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